

AMENDMENTSIn The Claims

83. (Amended) A transgenic nonprimate mammal comprising in its germline a modified genome wherein said modification comprises a [lesion in] deletion of all or substantially all of the J region of at least one copy of the immunoglobulin heavy chain locus, wherein said <sup>deletion</sup> ~~lesion~~ results in the inability of said copy of the locus to rearrange or to produce a functional message encoding an immunoglobulin heavy-chain subunit.

REMARKSAmendment To The Claim

This amendment to claim 83 is made to facilitate prosecution, and without prejudice to Applicants' rights to pursue broader claims in a divisional application. No new matter is added by this amendment.

The Invention

The invention relates to production of transgenic mammals that have been genetically manipulated so as not to express endogenous immunoglobulin heavy chain genes. Mammals that have had heavy chain immunoglobulin gene expression inactivated are extremely useful because unrearranged human immunoglobulin genes may be inserted into the genomes of such mammals to express essentially human antibodies.

Immunoglobulin gene loci are large and highly complex. The heavy chain locus is particularly large and complex. The unrearranged heavy chain locus consists of three major regions, each region containing multiple genes. There is the heavy chain V region. In mice, the V region comprises about 100 different V genes. There is also the heavy chain D region. In mice, the J region comprises about 12 different D genes. There is also the heavy chain J region. In mice, the J region comprises about 4 different J genes. There is also the heavy chain C region. In mice, the C region comprises